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Factors determining the magnitude of the pre-ejection leftward septal motion in left bundle branch block

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Aims

An abnormal large leftward septal motion prior to ejection is frequently observed in left bundle branch block (LBBB) patients. This motion has been proposed as a predictor of response to cardiac resynchronization therapy (CRT). Our goal was to investigate factors that influence its magnitude.

Methods and results

Left (LVP) and right ventricular (RVP) pressures and left ventricular (LV) volume were measured in eight canines. After induction of LBBB, LVP and, hence, the transmural septal pressure ($P_{LV-RV} = LVP - RVP$) increased more slowly ($P < 0.01$) during the phase when septum moved leftwards. A biventricular finite-element LBBB simulation model confirmed that the magnitude of septal leftward motion depended on reduced rise of P_{LV-RV} . The model showed that leftward septal motion was decreased with shorter activation delay, reduced global or right ventricular (RV) contractility, septal infarction, or when the septum was already displaced into the LV at end diastole by RV volume overload. Both experiments and simulations showed that pre-ejection septal hypercontraction occurs, in part, because the septum performs more of the work pushing blood towards the mitral valve leaflets to close them as the normal lateral wall contribution to this push is lost.

Conclusions

Left bundle branch block lowers afterload against pre-ejection septal contraction, expressed as slowed rise of P_{LV-RV} , which is a main cause and determinant of the magnitude of leftward septal motion. The motion may be small or absent due to septal infarct, impaired global or RV contractility or RV volume overload, which should be kept in mind if this motion is to be used in evaluation of CRT response.

Keywords

Left bundle branch block • Septal beaking • Dyssynchrony • Computer modelling • Ventricular function

Introduction

In left bundle branch block (LBBB), the septum tends to move leftwards into the left ventricle (LV) at onset of systole followed by a rightward motion towards the right ventricle (RV).¹ This abnormal septal motion has been referred to as both *septal beaking*, based on observations in echocardiographic M-mode images^{2,3} (Figure 1), and more recently as *septal flash*⁴ based on a characteristic colour

pattern in tissue Doppler images. In the latter study and in a more recent study,⁵ 89 and 88%, respectively, of the patients with this septal motion responded to cardiac resynchronization therapy (CRT). However, the underlying mechanisms that determine the magnitude of the early systolic septal motion in LBBB are not fully understood. An improved mechanistic understanding underpinning this motion is of clinical interest due to its potential as a predictor for CRT response.

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What's new?

- This study investigates in detail factors that influence the magnitude of the abnormal pre-ejection leftward septal motion in left bundle branch block including the role of ventricular pressures, changes in contractility, septal infarction, activation delay, right ventricular (RV) volume overload, and the closing motion of the mitral valve leaflets.
- The magnitude is highly dependent on slowed early systolic rise in left ventricular pressure (LVP) and hence slowed rise of transmural septal pressure ($LVP - RVP$).
- The magnitude is reduced with a decrease in septal to left ventricular lateral wall activation delay, septal infarct, impaired global or RV contractility, or RV volume overload.
- The pre-ejection septal hypercontraction occurs, in part, because it does more of the work to push blood towards the closing mitral valve leaflets during the phase when the leaflets are pushed towards the atrium, as the normal lateral wall contribution to this push is lost.

The position of the inactivated septum and septal segment length have been shown to be determined by the right (RVP) and left ventricular (LVP) pressures at end diastole (ED).^{6–8} Previous studies, where RV apical pacing was used as a model for LBBB, reported a reversal of the transmural septal pressure ($P_{LV-RV} = LVP - RVP$) at onset of systole due to the earlier RV than LV activation, thus suggesting a pressure mediated pre-ejection leftward motion of the septum.^{3,7} We recently proposed that the septum actively contracts into the LV as most of the leftward motion occurs during a rise in P_{LV-RV} as seen in canines with LBBB.⁹ Even though there is a rise in P_{LV-RV} during leftward motion, the rate of rise may be slower than normal, which effectively reduces the instantaneous afterload to the contracting septum. The relation between early systolic rise in P_{LV-RV} and leftward septal motion in LBBB is not known. Since a reduction in afterload increases shortening velocity, we hypothesize that the magnitude of the leftward motion depends on the reduction in the rise of P_{LV-RV} .

We also hypothesize that the magnitude of leftward septal motion depends on other factors such as changes in regional and global contractility including septal infarction, LV septal-to-lateral wall activation delay, and RV volume overload where the septum is already displaced into the LV at ED. Furthermore, if the septum moves into the LV during the isovolumic contraction phase, other structures have to stretch. Previous studies have suggested that this motion of the septum is made possible by the simultaneous stretching of the late-activated LV lateral wall.^{9,10} However, there may also be stretching of other LV regions that facilitate the leftward septal motion which has not been previously considered. During the pre-ejection phase, the mitral valve leaflets are pushed closed and moved towards the left atrium until they reach their final closed position when the papillary muscles and chordae tendineae become completely taut, implying that there is blood moving behind the closing leaflets. We previously found that ~5% of the volume from apex to equator was pushed towards the valve plane during mitral valve closure in the normally electrically activated LV.¹¹ The

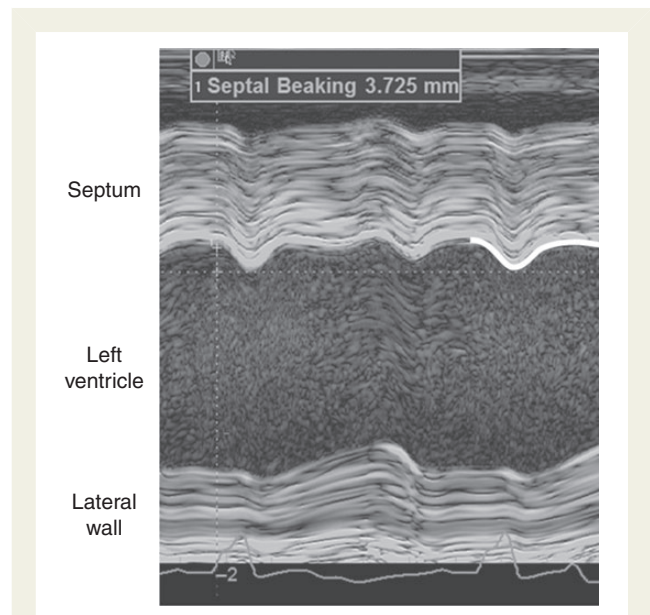


Figure 1 M-mode image from an animal with LBBB. In the left heartbeat, the calliper function has been used to quantify the magnitude of early systolic leftward septal motion (~3.7 mm in this example). In the right beat, the LV endocardial border has been drawn with thick white line for comparison with traces in Figures 2 and 4.

septal as well as anterior, lateral, and posterior LV regions all shortened during this phase. Hence, only a small amount of shortening was needed in each of these regions to push 5% of the blood from apex to base. We hypothesize that due to late activation, the LV free wall contribution to this push is lost in LBBB and that a component of the abnormally large leftward septal motion is the earlier activated septum moving further leftwards to compensate for this loss as septum mostly alone pushes all the blood required to move the leaflets to their closed position.

The aim of this study was to investigate factors that influence the magnitude of the abnormal septal leftward motion at the beginning of systole in LBBB. Focused on this goal, we have analysed ventricular pressures and the apical volume reduction together with regional deformations during mitral valve closure at baseline and after induction of LBBB in canines. We further applied a mathematical finite-element (FE) model of the ventricles where ventricular pressures, volumes, and activation sequence could be altered in an isolated and controlled manner. In this model, we tested how P_{LV-RV} , changes in contractility including septal infarction, LV septal-to-lateral wall activation delay, RV volume overload, and the closing of the mitral valve influenced the magnitude of leftward early systolic septal motion.

Methods

Experimental study

We analysed measurements from a previously performed acute experimental study on eight mongrel canines (34 ± 2 kg).⁹ The study was

approved by the Norwegian Animal Research Authority and confirmed to the guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes. The animals were supplied by Centre for Comparative Medicine, Oslo University Hospital, Oslo, Norway. The animals were anesthetized with a bolus of thiopental 25 mg/kg, followed by continuous infusion of morphine ($3.5 \text{ mg kg}^{-1} \text{ h}^{-1}$) and pentobarbital ($2 \text{ mg kg}^{-1} \text{ h}^{-1}$). Pentobarbital was reduced to half the dose after 4 h of infusion. The animals were artificially ventilated through a cuffed endotracheal tube with room air and 20–50% oxygen. At completion of the experiment, the animals were euthanized by an overdose of pentobarbital injected directly into the LV.

The surgical preparation, instrumentation, and interventions have been described in detail previously.⁹ In brief, this was an open-chest model with loosely resutured pericardium following surgical instrumentation of the heart. Left atrial and left and right ventricular and aortic pressures were measured by micromanometers (MPC-500, Millar Instruments, Inc., Houston, TX). Left ventricular dimensions and regional deformations were measured by sonomicrometry (Sonometrics Corporation, London, Ontario, Canada). Regional electrical activation times were recorded from implanted bipolar electrodes. Data were recorded at 200 Hz. Recordings were obtained at baseline and following induction of LBBB. Left bundle branch block was induced by radiofrequency ablation (Celsius Catheter, Biosense Webster, Inc.). Stable LBBB was obtained after 5–20 ablations ($50^\circ\text{C}/30 \text{ W}$) at a location with a large left bundle potential, two-thirds from the atrial and one-third from the ventricular signal. Energy was delivered for 30 additional seconds after induction of LBBB.

The LV volume from equator to apex was calculated using sonomicrometric crystals. Four crystals were placed subendocardially around the equator (two-thirds the distance from apex to base) in the septum, anterior, lateral, and posterior LV walls and one at the apex. The average long-axis diameter from apex to these four equatorial crystals was assessed. This long-axis diameter and two short-axis diameters were used to calculate the apical two-thirds of the LV volume (LVV apical) as shown in the following equation:¹²

$$\text{LVV apical} = \pi/6 \times \text{septum-to-lateral wall diameter} \\ \times \text{anterior-posterior wall diameter} \times \text{long-axis diameter}$$

Strain was assessed between crystal pairs aligned in the circumferential and longitudinal directions in both septum and LV lateral wall. We further calculated leftward septal motion as the displacement of the septal equatorial crystal into the LV,¹³ qualitatively similar to tracking the displacement of the LV endocardial septal border as shown in the M-mode image in Figure 1. We investigated deformations during early systole from onset Q in electrocardiogram (ECG) to the end of mitral valve closing (MVC) phase, which is seen as the c-wave in the LA pressure trace (Figure 2). The c-wave has been attributed to the closing motion of the mitral leaflets towards the LA, which temporarily increases LA pressure.¹⁴

Mathematical model study

We applied the RV and LV FE modelling framework previously applied to a study of human hearts with LBBB.¹⁵ The online supplement of that article describes the mathematical modelling concepts in detail. In short, the geometry was modified to a generic circular LV shape (Figure 3) with dimensions representative of a typical dog heart: LV short- and long-axis diameters of 4 and 6 cm, respectively, and an LV equatorial wall thickness of 8 mm. The transmural fibre orientation was interpolated linearly from 90° with respect to the circumferential orientation at the endocardium to -60° at the epicardium, in qualitative agreement with

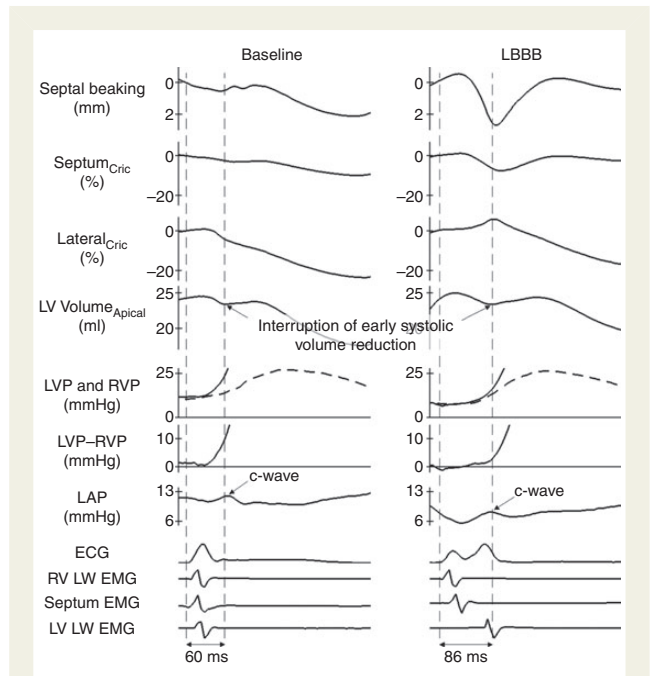


Figure 2 Representative recordings during early systole from an animal before and after induction of LBBB. LV Volume_{Apical} is the measured volume from equator to apex. The dashed vertical lines mark the time interval from onset Q in the ECG to interruption of early systolic reduction of LV Volume_{Apical} associated with apical blood volume pushed towards the base to complete the closing motion of the mitral valve. LV, left ventricular; RV, right ventricular; Septal beaking, displacement of the sonomicrometric crystal in the septum towards the centre of the LV, corresponding to M-mode motion in Figure 1; Septum_{Circ} and Lateral_{Circ}, circumferential strain in septum and LV lateral wall, respectively; LVP, LV pressure; RVP, RV pressure; LAP, left atrial pressure; LW, lateral wall; EMG, electromyogram.

measured data.¹⁶ Electrical activation was simulated using the monodomain equations with initial stimulation sites in the subendocardial region around the mid third below the equator of both ventricles for normal activation and only in the RV for LBBB activation. Conduction velocity was adjusted to fit the septal to LV lateral wall activation delay at equator to the measured delay between electrodes at these two sites during LBBB in the animals (Figure 3).

Passive elastic properties were defined by a transversely isotropic material law aligned to the fibre orientation using similar stiffness parameters as in the previous study.¹⁵ Furthermore, we applied the same length- and time-dependent active tension model where we adjusted the parameter for peak isometric tension to 100 kPa, giving a maximum LV dP/dt of 1500 mmHg/s consistent with measurements in the animals. Prior to activation, the LV and RV were inflated to end diastolic pressures of 9.0 and 7.5 mmHg, respectively. Following activation, the cavity volumes were kept constant as active fibre stress was increased according to the active tension model and regional activation times. At the time when LV and RV pressures exceeded 57 mmHg (average aortic pressure at onset ejection in the animals during LBBB) and 20 mmHg, respectively, ejection was simulated by Windkessel models providing the pressure–volume relations.¹⁵ The leftward septal motion occurred during the beginning of isovolumic contraction. Thus, simulation of ejection and the remainder of the cardiac cycle was of limited interest for this study.

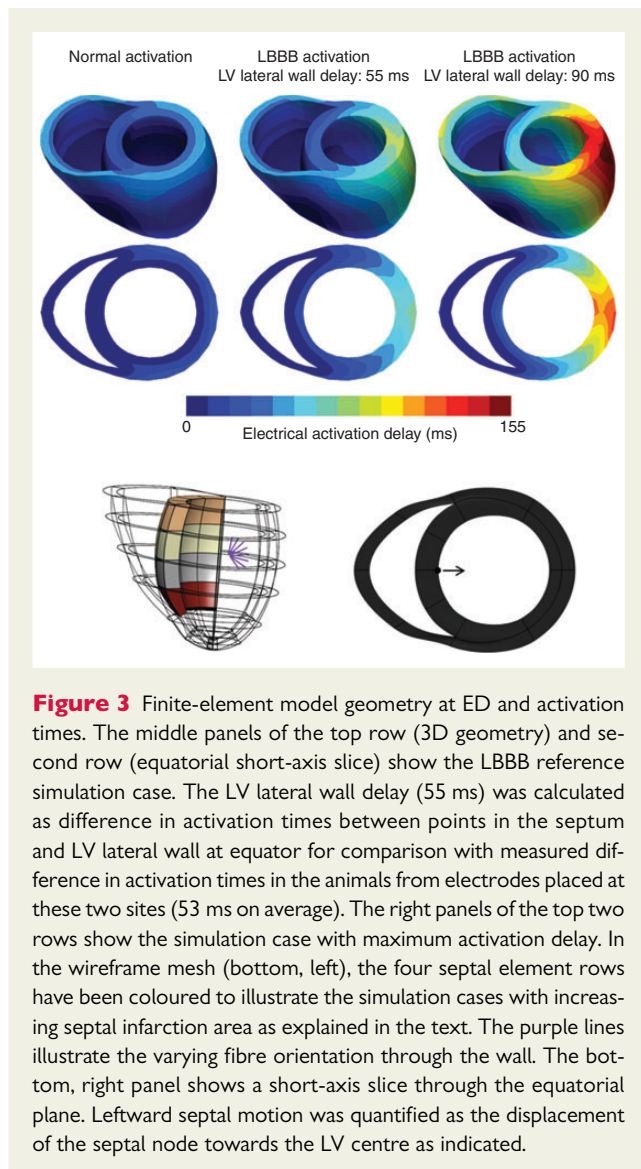


Figure 3 Finite-element model geometry at ED and activation times. The middle panels of the top row (3D geometry) and second row (equatorial short-axis slice) show the LBBB reference simulation case. The LV lateral wall delay (55 ms) was calculated as difference in activation times between points in the septum and LV lateral wall at equator for comparison with measured difference in activation times in the animals from electrodes placed at these two sites (53 ms on average). The right panels of the top two rows show the simulation case with maximum activation delay. In the wireframe mesh (bottom, left), the four septal element rows have been coloured to illustrate the simulation cases with increasing septal infarction area as explained in the text. The purple lines illustrate the varying fibre orientation through the wall. The bottom, right panel shows a short-axis slice through the equatorial plane. Leftward septal motion was quantified as the displacement of the septal node towards the LV centre as indicated.

We ran series of simulation cases within which model parameters were adjusted to quantify their effect on septal motion during early systole. Leftward septal motion was quantified as the displacement of an LV endocardial septal node towards the centre of the LV at the equatorial plane (Figure 3) to mimic assessment of this motion in M-mode images (Figure 1).

Reference simulations

Initially, we ran simulations with normal activation and LBBB activation where the ventricular volumes were enforced to be isovolumic from onset of activation (time = 0).

Transmural septal pressure

In the experiments, we observed that P_{LV-RV} had risen to a lower value at the time of peak leftward septal motion during LBBB compared with the same phase at baseline. In the simulation model, we investigated the magnitude of leftward motion with respect to variations in the level of P_{LV-RV} at time of peak septal leftward motion. The model is a steady-state model; thus, it is not dependent on the time course of P_{LV-RV} to a given level at a given time. Therefore, changing P_{LV-RV} at a specified time is equivalent to a change in the rise of P_{LV-RV} to this time point. P_{LV-RV} at the time of peak leftward motion of the reference

simulation was altered by changing RVP, while LVP was adjusted accordingly to maintain constant LV volume. This ensured that a potential increase or decrease in leftward septal motion would be caused by a change in P_{LV-RV} and not by a change in LV volume. However, the change in RVP changed RV volume during this isovolumic contraction phase. It must therefore be regarded as a hypothetical simulation case designed to illustrate the principle of the impact of P_{LV-RV} on magnitude of leftward septal motion.

Changes in contractility

In order to investigate the effect of changes in P_{LV-RV} while maintaining both cavity volumes constant during the isovolumic contraction phase, we performed four simulations where either RV or LV free wall contractility was changed by $\pm 50\%$. Mainly, the pressure rise in the ventricle with altered contractility would change, affecting rise in P_{LV-RV} . Changes in contractility were implemented by adjusting the parameter for peak isometric tension in the active tension model¹⁵ to 50 or 150 kPa in the free wall elements.

In order to investigate the effect of globally reduced or increased contractility, we performed two additional simulations with a similar $\pm 50\%$ contractility change in both ventricles including septum.

Septal infarction

We investigated the influence of septal infarction and varying infarct size. The infarcted region was modelled by stiff, isotropic properties that did not generate active fibre stress as explained previously.¹⁵ The septal wall consisted of four rows of elements from base towards apex (Figure 3). Four simulation cases were run. In the first, the most apical septal row of elements was infarcted; in the second, the two most apical septal rows were infarcted; in the third, the three most apical rows were infarcted; and in the final, all four rows (i.e. the entire septum) were infarcted.

Activation delay

The conduction velocity of electrical activation was initially estimated, so the LV septal-to-lateral wall activation delay was 55 ms for the reference LBBB simulation, consistent with the measured delay in the animals. We investigated the relation between magnitude of leftward septal motion and LV septal-to-lateral wall activation delay running simulation cases where this delay was altered from 20 to 90 ms by varying the electrical conduction velocity.

Right ventricular volume overload

We then investigated if the magnitude of pre-ejection leftward septal motion was reduced if the septum was already pre-displaced leftwards at ED, which occurs in RV volume overload when ED RVP is increased and hence ED P_{LV-RV} decreased. In different simulation cases, ED RVP was increased in steps of 0.75 mmHg, so ED P_{LV-RV} changed from 1.5 mmHg at the reference simulation to -5.25 mmHg. This displaced the ED septal position leftwards as ED RV volume was increased.

Closing of the mitral valve

During the beginning of systolic contraction, there is an LV intracavitary redistribution of blood from the apical to basal region as the mitral valve leaflets move towards the atrium during valve closure. The simulation model did not include the mitral valve leaflets. Thus, we could not directly simulate the closing motion of the leaflets. However, the effect of mitral valve closure could be simulated by changing LV apical volume accordingly. Incorporating a 5% reduction of the volume from apex to equator during the beginning of contraction infers a reciprocal increase in the volume encapsulated within the basal segments and hypothetical mitral leaflets as they would move in the direction of the left atrium. Consistent with our experimental measurements, we reran the normal

Table 1 Changes during interval from onset Q in ECG to end of mitral valve closure ($n = 8$)

	Baseline	LBBB
Duration of interval, ms	65 ± 8	$83 \pm 15^*$
Δ LVP, mmHg	18.0 ± 7.1	$8.9 \pm 4.5^*$
ΔP_{LV-RV} , mmHg	14.3 ± 6.6	$3.6 \pm 2.6^*$
Δ LVV apical, %	-5.0 ± 2.6	-4.2 ± 2.6
Septal circ strain, %	-3.0 ± 2.2	$-7.7 \pm 5.6^*$
Septal long strain, %	0.4 ± 2.1	-2.1 ± 2.3
LV lateral wall circ strain, %	-2.7 ± 1.4	$3.2 \pm 3.1^*$
LV lateral wall long strain, %	-0.9 ± 1.2	$2.1 \pm 1.7^*$

LV, left ventricular; LVP, LV pressure; P_{LV-RV} , transmural septal pressure; LVV apical, LV volume from apex to equator; circ, circumferential; long, longitudinal. $*P < 0.02$.

and LBBB activation reference simulations incorporating a 5% reduction of the LV volume from equator to apex. Implementation of the early systolic apical volume reduction was achieved by controlling the pressure relative to the volume: active myocardial fibre tension increases for each new time step. To maintain a constant volume, the cavity pressure must increase correspondingly, while a smaller pressure increase will result in a volume reduction. Left ventricular pressure was controlled to follow a specified linear pressure–apical volume relation with a 5% apical volume reduction as LVP rose from 9 to 22 mmHg, similar to the experimental findings. During the remaining time steps of the pre-ejection phase, LVP was increased to maintain global LV isovolumic conditions. We further performed a series of simulations with LBBB activation where the magnitude of this volume reduction was varied to investigate its relation to the magnitude of leftward septal motion.

Statistics

Experimental results are presented as mean \pm SD. For comparisons between values from baseline and LBBB, we applied a two-tailed, paired Student's *t*-test, where $P < 0.05$ was considered significant.

Results

Experimental canine study

Induction of LBBB caused electrical dyssynchrony and abnormal deformation as shown in Figure 2. There was an increase in QRS duration (112 ± 4 vs. 59 ± 8 ms at baseline, $P < 0.01$). The LV lateral wall was activated 53 ± 10 ms after septum, which was significantly different from the delay at baseline (9 ± 5 ms, $P < 0.01$). Both during baseline and LBBB, there was an early systolic contraction of the LV apical volume that was interrupted when the mitral valve finished its closing movement (c-wave in LAP trace). As shown in Figure 2 and Table 1, this interval was prolonged and LVP rise was slowed with LBBB, consistent with less efficient global LV contraction. While both the septum and LV lateral wall shortened moderately during this phase at baseline, the LV lateral wall lengthened during LBBB while shortening in the septum increased substantially (Table 1). The early systolic reduction in LV apical volume was relatively similar during baseline and LBBB. This indicates that the septum is doing more of the work, i.e. increased septal shortening, to push blood from the apical LV region towards the valve plane during mitral valve closure.

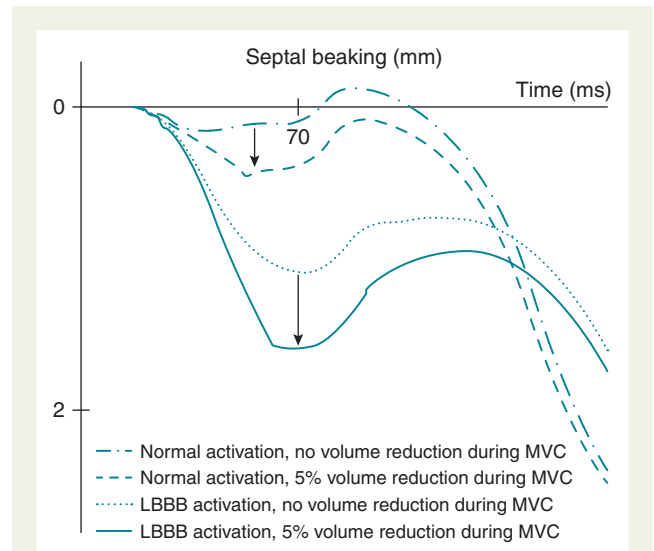


Figure 4 Simulation results: early systolic leftward displacement of the septum, mimicking septal beaking M-mode traces as shown in Figure 1. Left bundle branch block activation resulted in substantial leftward motion. As indicated by the downward arrows, the leftward motion was increased in the simulation cases when LV apical volume was reduced by 5% to simulate the blood volume that is pushed towards the basal region during the MVC phase. As can be seen, this increase was larger during LBBB activation than normal activation, despite the displaced blood volume being identical. The larger increase in leftward motion is thus consistent with the septum doing more of the work to push this blood volume towards the closing mitral valve in LBBB.

Mathematical model study

Reference simulations

In the LBBB activation simulation case, the model reproduced the typical early systolic septal leftward motion followed by rightward motion. Figure 4 shows septal motion for normal and LBBB activation.

Transmural septal pressure

The magnitude of leftward septal motion was highly dependent on the simultaneous rise in P_{LV-RV} . Figure 5A shows the relation between the magnitude of P_{LV-RV} at the time of peak leftward septal motion and magnitude of the septal motion for the simulation cases where P_{LV-RV} at time of peak leftward motion was adjusted. Septal leftward motion was 1.1 mm in the reference simulation. From the slope of the relation in Figure 5A, it can be inferred that leftward motion was increased by ~ 0.2 mm per 1 mmHg reduced rise in P_{LV-RV} .

Changes in contractility

Reduced RV free wall contractility slowed RVP rise, increasing the rise in P_{LV-RV} by 3.3 mmHg during the first 70 ms, thus decreasing leftward septal motion. The effect was opposite for increased RV contractility. Reduced contractility in the LV free wall slowed the rise in P_{LV-RV} by 3.0 mmHg and hence increased leftward septal motion and vice versa (Figure 5A).

Global 50% reduced contractility decreased leftward septal motion to 0.8 mm (i.e. 27% decrease), while it was increased to 1.3 mm

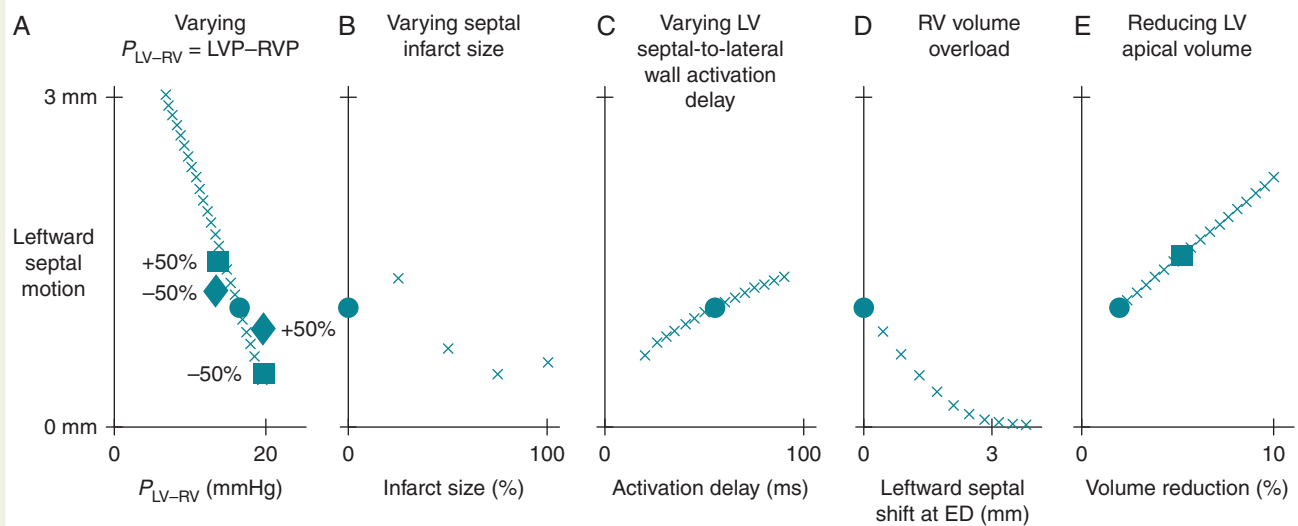


Figure 5 Pre-ejection leftward septal motion as a function of five different variables in the simulation model. The bullet point represents the reference LBBB simulation case in all panels. (A) The transmural septal pressure (P_{LV-RV}) at the time of peak leftward septal motion was varied. The two square points are the simulation cases when RV free wall contractility was reduced or increased by 50%. The two diamond points are the cases for similar changes in LV free wall contractility. (B) Simulation cases when a septal infarct was included in the model and infarct region was stepwise increased to cover the most apical row of septal elements (25%), the 2 most apical rows (50%), the 3 most apical rows (75%), and all 4 rows (100%). (C) Simulation cases where activation delay between septum and LV lateral wall was varied. (D) End diastolic (ED) position of the septum was shifted leftwards by increasing ED RV pressure and volume. (E) Left ventricular apical volume was reduced to different degrees to simulate the MVC phase. The square point is the simulation case when this volume was reduced by 5%, which was similar to the average volume reduction in the animals. In the default LBBB simulation case (bullet point), the global LV volume is constant. Still there is a slight reduction in apical volume (1.8%), which is explained by this volume being pushed from apex to the late-activated basal region that stretches during this phase.

(18% increase) with 50% increased contractility. The time to peak leftward motion was prolonged with reduced contractility, but the rise in P_{LV-RV} was slower, resulting in a similar P_{LV-RV} at this time point.

Septal infarction

In all three simulation cases when the equatorial septal elements were infarcted, leftward motion was decreased (Figure 5B). However, when only the most apical row of septal elements was infarcted (25% septal infarction), there was a slight increase in the equatorial leftward septal motion, which was located more basal than the infarct region. The loss of contractile force in the apical part of septum resulted in these elements being pushed rightwards when the more basal part of septum actively contracted. Thus, the equatorial septum was allowed to move further leftward, pushing blood towards the stretching apical septal region in this simulation case. The rise in P_{LV-RV} was gradually reduced to only 1 mmHg with 100% septal infarct region. Despite this reduced afterload against leftward septal motion, leftward motion decreased as active septal contraction was gradually abolished by increasing septal infarct size.

Activation delay

Increased activation delay in the LV lateral wall relative to the septum, increased leftward septal motion (Figure 5C). When activation delay was increased from 20 to 90 ms, the leftward septal motion increased from 0.7 to 1.4 mm, and at the same time, the rise in

LVP was slowed down, resulting in a reduced rise of P_{LV-RV} by 6.3 mmHg.

Right ventricular volume overload

In simulation cases with increasing ED RVP and ED RV volume, the septum was substantially shifted into the LV at ED (Figure 5D). This resulted in a corresponding reduction in the subsequent pre-ejection leftward septal motion. In the cases with the most extreme ED leftward position of septum, there was practically no pre-ejection leftward motion following ED. In these cases, the septum started moving rightwards.

Closing of the mitral valve

As seen in Figure 4, leftward septal motion was increased when a 5% apical LV volume reduction was included to simulate the MVC phase both during normal and LBBB activations. However, as seen in the figure, this increase in leftward motion was 0.3 mm during normal activation, while the increase was 0.5 mm during LBBB activation, consistent with the septum contributing more to the mitral valve closure during LBBB. The reduction in LV apical volume and increased leftward septal motion were related to a reduced rise in LVP. This further reduced the rise in P_{LV-RV} by 2.3 and 4.9 mmHg for normal and LBBB activations, respectively, consistent with reducing afterload during this phase, thus allowing for more septal contraction. Figure 5E shows the relation between the magnitude of apical volume reduction during the MVC phase and magnitude of leftward septal motion.

Discussion

In our previous study,⁹ we found that in LBBB the septum actively contracted into the LV as opposed to being passively pushed in by the RVP rising faster than LVP. Furthermore, we found that the magnitude of this motion depended on the end diastolic P_{LV-RV} . In the present study, we investigated a number of additional factors that could influence the magnitude of early systolic septal leftward motion in LBBB, which is important if it is to be used as a clinical predictor of response to CRT. In particular, it would be of clinical interest to understand what factors could reduce or abolish this motion despite the presence of LBBB. We identified that the magnitude of this motion is highly dependent on slowing of the rise of LVP and P_{LV-RV} , which is consistent with the slowed rise in P_{LV-RV} representing a reduced instantaneous afterload to contraction of the septum into the LV. We also showed that increased septal to LV lateral wall activation delay increases leftward septal motion, while reduced global or RV contractility or septal infarction reduces it, and that an already leftward displaced septum at ED due to RV volume overload reduces the pre-ejection leftward motion following ED. Previously, it has been suggested that the abnormally large septal motion into the LV is facilitated by stretching of the late-activated LV lateral wall. However, we demonstrated that the closing motion of the mitral leaflets towards the atrium also facilitates increased leftward septal motion. This is due to the septum almost alone is doing the work to close the valve: the septum pushes all the blood from the apex towards the valve leaflets in order to push them to their closed position with limited or even paradoxical contribution to this push from the LV free wall.

Transmural septal pressure

Late activation of the LV lateral wall delays active contraction in this region, which temporarily impedes its contribution to increasing LVP. In the animals, we found that the abnormally large leftward septal motion occurred as the simultaneous rise in LVP and P_{LV-RV} was significantly reduced. This reduced rise in P_{LV-RV} offered reduced instantaneous afterload against septal contraction and leftward motion compared with the quicker rise in P_{LV-RV} during normal activation. It is important to note that instantaneous afterload here refers to the afterload during the beginning of systole when LVP is typically <30 mmHg, and not afterload in the more conventional sense as peak LVP during ejection. Model simulations confirmed the high sensitivity of leftward septal motion to alterations in P_{LV-RV} during the same interval. Thus, leftward septal motion is not a response to a reversal of P_{LV-RV} as previously proposed,^{6,7} but rather a reduced rise of P_{LV-RV} .

Changes in contractility

Left bundle branch block is often associated with cardiomyopathy with reduced contractility. In the simulation model, reduced global contractility reduced leftward septal motion and vice versa. Instantaneous afterload (P_{LV-RV}) at the time of peak leftward motion was unaltered; hence, the changes in motion reflected changes in contractility consistent with an active contraction component to the leftward septal motion.

Septal infarction

The distinct early systolic leftward motion of the septum may not be seen in all LBBB patients. As the majority of the septal leftward motion is caused by active septal contraction,⁹ septal infarction, which impairs active septal contraction, should reduce leftward septal motion. This was supported by the simulation model results where the leftward motion was reduced when septal infarction was included. These findings are consistent with inspection of the septal fibre shortening traces shown by Leenders *et al.*¹⁷ (in their *Figure 4*) where they reduced septal contractility in the CircAdapt model. It is also noteworthy that in one of the original studies of septal motion and LBBB, Dillon *et al.*² reported that the characteristic abnormal pre-ejection septal motion was observed in all LBBB cases with the exception of the two patients who also had coronary artery disease.

Activation delay

We found that increased LV septal-to-lateral wall activation delay increased leftward septal motion. Leenders *et al.*¹⁷ did not explicitly investigate the magnitude of leftward septal motion; however, they varied mechanical activation delay in their CircAdapt mathematical model of an LBBB heart. In *Figure 3* in their paper, increased septal fibre shortening can be seen with increasing delay, consistent with our findings.

Right ventricular volume overload

When end diastolic RVP, and consequently volume, was increased, the septum was displaced leftwards at ED. This resulted in a flattening of the septal wall, i.e. increased septal radius of curvature. In our previous experimental study,⁹ we constricted the pulmonary artery to create RVP overload; however, this also resulted in ED RVP increase and an ED leftward shift and flattening of the septum. Leftward septal motion following ED was reduced in that case, consistent with the simulation results in the current study. The wall stress in a circular LV wall generates a perpendicular traction acting on the surface, which is in equilibrium with the cavity pressure. As active wall stress increases, the wall contracts and moves or squeezes inward, increasing cavity pressure which maintains this equilibrium. A flatter septum will generate a lower surface traction, in keeping with Laplace's law. Inward septal contraction will be resisted with a lower cavity pressure, hence reducing the magnitude of leftward motion. When the septum is flattened (has a large radius of curvature) relative to the LV free wall, the cavity pressure will increase faster than the surface stress developed by active contraction in this septal configuration. The septum will move rightwards becoming more curved (lower radius of curvature), so the surface traction matches the cavity pressure. We believe that this principle also explains the subsequent rightward septal motion (or the so-called rebound stretch) that normally follows the initial leftward motion and flattening of the septum in LBBB.

Closing of the mitral valve

Our study shows that leftward septal motion is not only facilitated by LV lateral wall stretch but also by the closing motion of the mitral valve, a factor that, to our knowledge, has not been proposed before. Analogous to how late activation of the lateral wall increases

effective chamber compliance during early systole and hence reduces LV pressure rise, early systolic flexible motion of the mitral leaflets also effectively increases chamber compliance, reducing the rate of pressure rise and afterload during this phase, as opposed to if they had been completely rigid. The closing motion of the leaflets towards the atrium implies that there is a volume of blood displaced behind the leaflets. Furthermore, displacement of blood implies a connected wall displacement. In the animals during normal activation, there was a small, synchronous shortening in the whole LV wall from apex to equator that reduced the apical volume by $\sim 5\%$ during the closing motion of the mitral valve. This is consistent with activation¹⁸ and contraction of the LV apical region prior to the basal region.

The reduced apical blood volume represents the blood that is pushed towards the closing mitral valve. Also during LBBB activation, there was a similar apical volume reduction. This supports the notion that a given volume displacement from the apical region towards the valve is required to push the valve shut independent of activation sequence. During LBBB, the late-activated LV lateral wall did not contribute to this apical volume reduction as it was simultaneously stretching instead of shortening. Hence, the early-activated septum pushed blood both against the LV lateral wall and towards the basal LV region. Thus, our results suggest that a contributing factor for early systolic septal hypercontraction during LBBB is that the septum does more of the work to move the blood required to close the mitral valve. It is important to note that the closing motion of the mitral valve does not imply there is retrograde flow into the atrium as the mitral leaflets may coapt before or at the beginning of the motion. The apical blood volume that is pushed towards the base is encompassed by the flexible motion of the leaflets, and potentially also stretching of the later-activated basal segments, until the chordae tendineae and segments become completely tense and stop stretching. Left bundle branch block is associated with increased risk of mitral valve regurgitation.¹⁹ Thus, it is possible that if early systolic apical blood volume is reduced even more by retrograde flow through the mitral valve, leftward septal motion may be further amplified, consistent with the relation shown in Figure 5E.

Clinical implications

As abnormal pre-ejection septal motion may be a potential predictor of response to CRT,^{4,5} it is important to understand the underlying mechanisms that determine the magnitude of this motion. The proposed factors in this study may vary in different clinical states. The early systolic rise in P_{LV-RV} substantially influences the magnitude of the motion. Increased LV lateral wall activation delay slows the rise in P_{LV-RV} as well as allowing a greater and more prolonged stretch of the LV lateral wall, thus amplifying the leftward septal motion and vice versa. Clinically, response to CRT depends on the QRS width, which reflects this delay. Furthermore, reduced RV contractility decreased leftward septal motion by reducing RVP rise and hence increasing rise in P_{LV-RV} . Leftward motion was also decreased by globally reduced contractility, a condition clinically relevant for cardiomyopathy often associated with LBBB. Since the closing motion of the mitral valve leaflets towards the left atrium facilitates part of the septal motion into the LV, mitral insufficiency may increase the amplitude of the leftward motion, while mitral stenosis may have the opposite effect. However, confounding factors with valve

disease such as changes in loading or remodelling may counteract or obscure this predicted effect on septal motion. Pulmonary regurgitation may cause RV volume overload and ED septal flattening that will reduce pre-ejection leftward septal motion. Left bundle branch block may be a result of septal infarction. Thus, an infarct that causes LBBB may also be a factor that reduces the abnormal leftward septal motion, precluding the use of this motion as a diagnostic marker of LBBB. This study has been limited to abnormal septal motion during the pre-ejection phase in LBBB. However, there may also be abnormal septal motion during other phases¹⁷ in LBBB and also in other disease conditions such as pulmonary hypertension. Some of the factors investigated in the present study may be relevant to explain the abnormal septal motion also in those cases.

Limitations

Though the FE model includes advanced mathematical descriptions of the myocardium, it still is a simplified representation of the *in vivo* heart and contains a number of assumptions. The details of the FE model and assumptions have been described previously.¹⁵ The amplitude of the pre-ejection leftward septal motion in the simulations may be smaller than what can be observed in patients. However, this quantitative difference may in part be due to difference in heart size as the dimensions of our model were based on hearts from canines with a bodyweight of 34 ± 2 kg. Despite these limitations, the qualitative predictions of the model reflect septal motion and provide insight into how alterations in different input conditions such as pressures, volumes, contractility, and activation time affect septal motion.

Consistent with experimental findings, we included simulation of 5% LV apical volume displacement towards the valve plane during the closing motion of the mitral valve leaflets. It is possibly that a comparable volume displacement is also present in the RV during the closing motion of the tricuspid valve leaflets. No measurements are available to quantify the timing or magnitude of the change in RV volume during this phase. To test if the absence of this mechanism had a significant effect on septal motion, we performed a simulation with simultaneous 5% volume reduction in both RV and LV during this phase. The impact on the magnitude of leftward septal motion was small: the magnitude was 3% (0.05 mm) smaller compared with the simulation case (Figure 4, solid line) with only LV apical volume reduction.

Conclusions

The magnitude of the early systolic leftward septal motion in LBBB is highly dependent on pressure rise in the ventricles, where slowed LV pressure rise offers an abnormal low instantaneous afterload against leftward septal motion. The late activation of the LV lateral wall makes it compliant and thus facilitates a hyper leftward septal motion by stretching when the septum contracts. Another factor contributing to the abnormal leftward motion is that the septum almost alone, with no or limited contribution from the LV free wall, having to push all the blood required to move the mitral valve leaflets into their final closed position. Increased LV septal-to-lateral wall activation delay increases early systolic septal motion. The motion may be small or absent in the presence of septal infarct, impaired global or RV contractility or RV volume overload. This should be kept in mind if the early systolic septal motion pattern is to be used in evaluation of CRT response.

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